Chemistry of Natural Compounds, Vol. 50, No. 3, July, 2014 [Russian original No. 3, May–June, 2014]

SYNTHESIS OF FLAVONOID DERIVATIVES OF CYTISINE. 4. SYNTHESIS OF 3-ARYL-7-[2-(CYTISIN-12-YL)ETHOXY]COUMARINS

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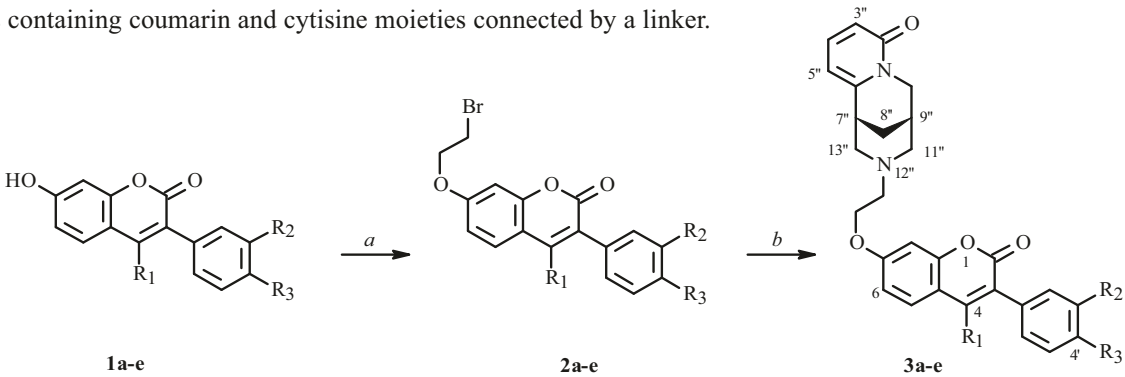
The possibility of using the alkaloid cytisine to synthesize N^{12}*-cytisinylethoxy 3-arylcoumarin derivatives was studied. A series of substituted 3-aryl-7-(*N^{12}*-cytisinylethoxy)coumarins with the coumarin and cytisine moieties connected by a linker were synthesized.*

Keywords: cytisine, coumarin, 2-(cytisine-12-yl)ethanol, alkylation.

Neuronal nicotinic acetylcholine receptors (nAChR) are interesting to many researchers because they are involved in complicated processes such as trainability, motivation, memory, attention, pain sensitivity, etc. Namely these functions are significantly impaired with aging and several neurodegenerative diseases (e.g., Alzheimer's, Parkinson's, schizophrenia). At present, nAChR are considered an interesting target for development of new drugs to treat CNS dysfunctions [1–3].

Cytisine exhibits high affinity for many nAChR subtypes, especially $\alpha_4\beta_2$ and α_3. However, its low lipophilicity hinders penetration through the blood–brain barrier (BBB) [2–5]. Therefore, a series of cytisine derivatives substituted in the N^{12} [6–12] and other positions [4, 5] were recently synthesized in order to discover new nAChR agonists or antagonists. Biological tests found that adding a substituent in the N^{12}-position decreased slightly the affinity for nAChR but allowed compounds with higher selectivity for the central $\alpha_4\beta_2$-subtype than for the α_3-subtype receptors to be prepared [11]. Furthermore, the analgesic, antiarrhythmic [13, 14], and antihypertensive activity [9] of N^{12}-substituted cytisine derivatives stimulated interest in developing new compounds of this series.

In our opinion, flavonoid cytisine derivatives are interesting as the combination of two pharmacophores in a single molecule with increased lipophilicity. This could enhance the passage of these compounds through the BBB. We synthesized previously various derivatives containing flavonoid and cytisine moieties connected by one or two methylenes in the 8-position or on O-7 of the chromone ring [15–17]. We chose 3-aryl-7-hydroxycoumarins for cytisine modification because they are a flavonoid subclass of biosynthetic origin. It was interesting to study the possibility of using this alkaloid to synthesize derivatives containing coumarin and cytisine moieties connected by a linker.



1a-e **2a-e** **3a-e**

a: $R_1 = R_2 = R_3 = H$; **b:** $R_1 = H$, $R_2 = R_3 = OMe$, **c:** $R_1 = R_2 = H$, $R_3 = Cl$
d: $R_1 = Me$, $R_2 = R_3 = OMe$, **e:** $R_1 = Me$, $R_2 = H$, $R_3 = Cl$

a. $BrCH_2CH_2Br$, K_2CO_3, DMF; *b.* cytisine, *i*-Pr_2NEt, EtOH

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 0009-3130/14/5003-0420

Starting substituted 3-aryl-7-hydroxycoumarins **1a**–**e** were obtained under Perkin reaction conditions via condensation of substituted phenylacetic acids with 2,4-dihydroxybenzaldehyde or 2,4-dihydroxyacetophenone in acetic anhydride in the presence of KOAc as the base with subsequent deacylation of the 7-acetoxy derivatives [18].

Alkylation of **1a**–**e** by an excess of dibromoethane in DMF in the presence of potash synthesized their corresponding 7-bromoethoxy derivatives **2a**–**e**.

The synthesis of 3-aryl-7-(*N*^{12}-cytisinylethoxy)coumarins **3a**–**e** was studied using the reaction of cytisine with **2a**–**e** in the presence of base. Cytisine was alkylated by **2a**–**e**, like for 7-(2-bromoethoxy)isoflavones [15], in high yield if the reaction was performed in EtOH in the presence of di-isopropylethylamine and produced **3a**–**e**. The product yields decreased if NEt_3 or *N*-methylmorpholine was used as the HBr acceptor because of quaternization of these bases. Alkylation of cytisine in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) formed coumarin vinyl ethers that complicated isolation and purification of the target compounds.

Thus, we synthesized a series of substituted 3-aryl-7-(*N*^{12}-cytisinylethoxy)coumarins containing coumarin and cytisine pharmacophores connected by a linker.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Sorbfil UV-254 (Russia) and Merck (Germany) plates using toluene–EtOH (9:1, 95:5) as eluent. PMR spectra were measured in $CDCl_3$ or DMSO-d_6 with TMS internal standard on the δ-scale on a VXR-300 instrument (Varian, 300 MHz). Elemental analyses of all compounds agreed with those calculated. Starting **1a**–**e** were prepared as before [18].

General Method for Synthesizing 3-Aryl-7-(2-bromoethoxy)coumarins 2a–e. A solution of **1a**–**e** (10 mmol) in DMF (20 mL) was treated with potash (25 mmol) and dibromoethane (50 mmol), stirred at 75–80°C for 3–5 h (end of reaction determined by TLC), and filtered to remove potash. The DMF was evaporated *in vacuo*. The residue was crystallized from *i*-PrOH–DMF.

7-(2-Bromoethoxy)-3-phenyl-2*H*-chromen-2-one (2a). Yield 65%, $C_{17}H_{13}BrO_3$, mp 150–151°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.86 (2H, t, ^{3}J = 5.0, $OCH_2\underline{CH_2}Br$), 4.46 (2H, t, ^{3}J = 5.0, $O\underline{CH_2}CH_2Br$), 7.02 (1H, dd, ^{3}J = 8.7, ^{4}J = 2.4, H-6), 7.07 (1H, d, ^{4}J = 2.4, H-8), 7.36–7.50 (3H, m, H-3′, 4′, 5′), 7.68–7.76 (3H, m, H-5, 2′, 6′), 8.21 (1H, s, H-4).

7-(2-Bromoethoxy)-3-(3,4-dimethoxyphenyl)-2*H*-chromen-2-one (2b). Yield 68%, $C_{19}H_{17}BrO_5$, mp 135–136°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.81 (6H, s, 3′, 4′-OMe), 3.84–3.91 (2H, m, $OCH_2\underline{CH_2}Br$), 4.42–4.52 (2H, m, $O\underline{CH_2}CH_2Br$), 6.98–7.10 (3H, m, H-6, 8, 5′), 7.23–7.37 (2H, m, H-2′, 6′), 7.69 (1H, d, ^{3}J = 8.9, H-5), 8.19 (1H, s, H-4).

7-(2-Bromoethoxy)-3-(4-chlorophenyl)-2*H*-chromen-2-one (2c). Yield 63%, $C_{17}H_{12}BrClO_3$, mp 165–166°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.85 (2H, t, ^{3}J = 5.2, $OCH_2\underline{CH_2}Br$), 4.47 (2H, t, ^{3}J = 5.2, $O\underline{CH_2}CH_2Br$), 7.02 (1H, dd, ^{3}J = 8.7, ^{4}J = 2.4, H-6), 7.08 (1H, d, ^{4}J = 2.4, H-8), 7.52 (2H, d, ^{3}J = 8.6, H-3′, 5′), 7.71 (1H, d, ^{3}J = 8.7, H-5), 7.76 (2H, d, ^{3}J = 8.6, H-2′, 6′), 8.26 (1H, s, H-4).

7-(2-Bromoethoxy)-3-(3,4-dimethoxyphenyl)-4-methyl-2*H*-chromen-2-one (2d). Yield 65%, $C_{20}H_{19}BrO_5$, mp 157–158°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 2.26 (3H, s, 4-CH_3), 3.75, 3.80 (3H each, s, 3′, 4′-OMe), 3.86 (2H, t, ^{3}J = 5.0, $OCH_2\underline{CH_2}Br$), 4.47 (2H, t, ^{3}J = 5.0, $O\underline{CH_2}CH_2Br$), 6.83 (1H, dd, ^{3}J = 8.1, ^{4}J = 2.0, H-6), 6.91 (1H, d, ^{4}J = 2.0, H-8), 6.98–7.08 (3H, m, H-2′, 5′, 6′), 7.75 (1H, d, ^{3}J = 8.1, H-5).

7-(2-Bromoethoxy)-4-methyl-3-(4-chlorophenyl)-2*H*-chromen-2-one (2e). Yield 61%, $C_{18}H_{14}BrClO_3$, mp 137–138°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.24 (3H, s, 4-CH_3), 3.86 (2H, t, ^{3}J = 5.2, $OCH_2\underline{CH_2}Br$), 4.47 (2H, t, ^{3}J = 5.2, $O\underline{CH_2}CH_2Br$), 7.0–7.08 (2H, m, H-6, 8), 7.35 (2H, d, ^{3}J = 8.2, H-3′, 5′), 7.51 (2H, d, ^{3}J = 8.2, H-2′, 6′), 7.78 (1H, d, ^{3}J = 8.7, H-5).

General Method for Synthesizing 3-Aryl-7-(*N*^{12}-cytisinylethoxy)coumarins 3a–e. A solution of the appropriate **2a**–**e** (2 mmol) in EtOH (30 mL) was treated with cytisine (2.4 mmol) and di-isopropylethylamine (3 mmol), refluxed for 14–18 h (end of reaction determined by TLC), cooled, and diluted with H_2O. The resulting precipitate was filtered off and crystallized from EtOH–H_2O.

(1*S*,5*R*)-3-{2-[(2-Oxo-3-phenyl-2*H*-chromen-7-yl)oxy]ethyl}-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3a). Yield 74%, $C_{28}H_{26}N_2O_4$, mp 164–165°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.65–1.85 (2H, m, CH_2-8″), 2.32–2.48 (3H, m, H-9″, 11″a, 13″a), 2.85–2.94, 2.97–3.07 (1H, 2H, 2m, H-7″, 11″b, 13″b), 3.65–3.85 (2H, m, CH_2-10″), 6.06 (1H, dd, ^{3}J = 7.0, ^{4}J = 1.4, H-5″), 6.18 (1H, dd, ^{3}J = 9.0, ^{4}J = 1.4, H-3″), 7.29 (1H, dd, ^{3}J = 9.0, ^{3}J = 7.0, H-4″); coumarin protons: 2.60–2.73 (2H, m, N$\underline{CH_2}CH_2$O-7), 4.00–4.14 (2H, m, $NCH_2\underline{CH_2}$O-7), 6.87 (1H, dd, ^{3}J = 8.4, ^{4}J = 2.4, H-6), 6.95 (1H, d, ^{4}J = 2.4, H-8), 7.36–7.50 (3H, m, H-3′, 4′, 5′), 7.71 (1H, d, ^{3}J = 8.4, H-5), 7.68–7.75 (2H, m, H-2′, 6′), 8.18 (1H, s, H-4).

(1*S*,5*R*)-3-(2-{[3-(3,4-Dimethoxyphenyl)-2-oxo-2*H*-chromen-7-yl]oxy}ethyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3b). Yield 70%, $C_{30}H_{30}N_2O_6$, mp 87–88°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.66–1.85 (2H, m, CH_2-8″), 2.32–2.47 (3H, m, H-9″, 11″a, 13″a), 2.84–2.92, 2.95–3.07 (1H, 2H, 2m, H-7″, 11″b, 13″b), 3.66–3.85 (8H, m, CH_2-10″, 3′, 4′-OCH_3), 6.06 (1H, dd, ^{3}J = 7.0, ^{4}J = 1.2, H-5″), 6.18 (1H, dd, ^{3}J = 9.0, ^{4}J = 1.2, H-3″), 7.25–7.37 (3H, m, H-4″, 2′, 6′); coumarin protons: 2.60–2.73 (2H, m, N-$\underline{CH_2}CH_2$O-7), 3.99–4.12 (2H, m, $NCH_2\underline{CH_2}$O-7), 6.86 (1H, dd, ^{3}J = 8.3, ^{4}J = 2.0, H-6), 6.94 (1H, d, ^{4}J = 2.0, H-8), 6.98–7.06 (1H, d, ^{3}J = 7.6, H-5′), 7.62 (1H, d, ^{3}J = 8.3, H-5), 8.15 (1H, s, H-4).

(1*S*,5*R*)-3-(2-{[2-Oxo-3-(4-chlorophenyl)-2*H*-chromen-7-yl]oxy}ethyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3c). Yield 77%, $C_{28}H_{25}ClN_2O_4$, mp 176–177°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.65–1.86 (2H, m, CH_2-8″), 2.29–2.47 (3H, m, H-9″, 11″a, 13″a), 2.85–2.93, 2.96–3.06 (1H, 2H, 2m, H-7″, 11″b, 13″b), 3.66–3.83 (2H, m, CH_2-10″), 6.05 (1H, dd, ^{3}J = 7.0, ^{4}J = 1.4, H-5″), 6.17 (1H, dd, ^{3}J = 9.0, ^{4}J = 1.4, H-3″), 7.29 (1H, dd, ^{3}J = 9.0, ^{3}J = 7.0, H-4″); coumarin protons: 2.59–2.76 (2H, m, N$\underline{CH_2}CH_2$O-7), 4.00–4.15 (2H, m, $NCH_2\underline{CH_2}$O-7), 6.87 (1H, dd, ^{3}J = 8.6, ^{4}J = 2.4, H-6), 6.95 (1H, d, ^{4}J = 2.4, H-8), 7.51 (2H, d, ^{3}J = 8.6, H-3′, 5′), 7.64 (1H, d, ^{3}J = 8.6, H-5), 7.75 (2H, d, ^{3}J = 8.6, H-2′, 6′), 8.23 (1H, s, H-4).

(1*S*,5*R*)-3-(2-{[3-(3,4-Dimethoxyphenyl)-4-methyl-2-oxo-2*H*-chromen-7-yl]oxy}ethyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3d). Yield 79%, $C_{31}H_{32}N_2O_6$, mp 103–104°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.69–1.86 (2H, m, CH_2-8″), 2.30–2.47 (3H, m, H-9″, 11″a, 13″a), 2.82–2.92, 2.95–3.09 (1H, 2H, 2m, H-7″, 11″b, 13″b), 3.63–3.86 (8H, m, CH_2-10″, 3′, 4′-OCH_3), 6.07 (1H, dd, ^{3}J = 7.0, ^{4}J = 1.5, H-5″), 6.20 (1H, dd, ^{3}J = 9.0, ^{4}J = 1.5, H-3″), 7.30 (1H, dd, ^{3}J = 9.0, ^{3}J = 7.0, H-4″); coumarin protons: 2.25 (3H, s, 4-CH_3), 2.62–2.74 (2H, m, N$\underline{CH_2}CH_2$O-7), 4.00–4.19 (2H, m, $NCH_2\underline{CH_2}$O-7), 6.79–7.04 (5H, m, H-6, 8, 2′, 5′, 6′), 7.70 (1H, d, ^{3}J = 8.4, H-5).

(1*S*,5*R*)-3-(2-{[4-Methyl-2-oxo-3-(4-chlorophenyl)-2*H*-chromen-7-yl]oxy}ethyl)-1,2,3,4,5,6-hexahydro-8*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one (3e). Yield 70%, $C_{29}H_{27}ClN_2O_4$, mp 99–100°C. ^{1}H NMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): cytisine protons: 1.65–1.84 (2H, m, CH_2-8″), 2.30–2.44 (3H, m, H-9″, 11″a, 13″a), 2.85–2.92, 2.96–3.07 (1H, 2H, 2m, H-7″, 11″b, 13″b), 3.65–3.81 (2H, m, CH_2-10″), 6.06 (1H, dd, ^{3}J = 7.0, ^{4}J = 1.4, H-5″), 6.18 (1H, dd, ^{3}J = 9.0, ^{4}J = 1.4, H-3″), 7.30 (1H, dd, ^{3}J = 9.0, ^{3}J = 7.0, H-4″); coumarin protons: 2.23 (3H, s, 4-CH_3), 2.61–2.74 (2H, m, N$\underline{CH_2}CH_2$O-7), 4.02–4.14 (2H, m, $NCH_2\underline{CH_2}$O-7), 6.89 (1H, dd, ^{3}J = 8.4, ^{4}J = 2.4, H-6), 6.95 (1H, d, ^{4}J = 2.4, H-8), 7.35 (2H, d, ^{3}J = 8.6, H-3′, 5′), 7.52 (2H, d, ^{3}J = 8.6, H-2′, 6′), 7.72 (1H, d, ^{3}J = 8.4, H-5).

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